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SPECIAL ISSUE ARTICLE

The deacetylase inhibitors—here to stay!

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The study of how cells control the transcription of genes is termed epigenetics. Epigenetics refers to heritable modifications in gene activities that do not involve changes in the DNA sequence. Epigenetic processes affect gene regulation and expression by changing the structure and conformation of DNA within chromatin which in turn can alter the ability of a gene to interact with transcription factors. Arguably the most widely studied area of epigenetics is gene methylation. The next most studied is histone modification—through affects on acetylation, methylation, phosphorylation, ubiquination and sumoylation. Of these histone modifications, acetylation status seems to be the most critical modification that dictates function. This acetylation status of the histone is determined by relative activity of two opposing enzyme families—the histone acetyltransferases (HATs) and the histone deacetylases (HDAC).

HDACs are classified by their homology to yeast HDACs. 18 are known, of which the eleven zinc-dependent metalloproteinases belong to class I, II, and IV. HDACs, usually in conjunction with other co-repressor enzymes, deacetylate lysine moieties in the tails of histones. The altered electrostatic charge leads to a relatively closed chromatin conformation and relatively repressed transcription.

As will be detailed in this series of manuscripts, the activity of the various members of these HDAC families can be inhibited by histone deacetylase inhibitors (HDACi). Before one considers the different types of HDACi, it is critical to recognize that these HDACi have targets well beyond nuclear histones—so called 'non-histone targets'. The recognition of this has led to a re-consideration of the terminology of these compounds. Consequently, they have been variably titled lysine-protein deacetylase inhibitors or more simply—deacetylase inhibitors (DACi). Such non-histone targets include p53, bcr-abl, HSP90, NFkB, HIF, bcl-6, STATs and other transcription factors/complexes, and the list goes on. Such targets will be discussed in depth in the various manuscripts to follow.

Through their histone affects, DACi are generally considered to be activators of transcription. However, gene expression profiling shows that as many genes may be repressed as upregulated after exposure to an histone DACi. This is a consequence of the direct and indirect effects of these drugs on other transcriptional regulators and cell signaling pathways. Taken together, such targeting directly on histones, transcription factors/complexes and non-histone targets, gives these drugs huge potential to be effective in a wide-range of cancers; there is also potential for substantial short- and long-term toxicities.

DAC inhibitors share a common pharmacophore containing a cap, connecting unit, linker and importantly a zinc binding group that chelates the cations (typically zinc) in the catalytic domain of the target HDAC and are currently classified according to their chemical structure and have variable ability to inhibit the deacetylase activity of specific HDACs as will be detailed throughout the various reviews. Indeed, not all DACi are the same! There are substantial differences between the various DACi drugs based not only on the targets for hyperacetylation (i.e. the different classes of HDACs targeted – pan-DACi vs. isotype specific DACi) but also the capacity to hyperacetylate lysine residues on histones and non-histone target, as well as their individual pharmacokinetic properties (oral vs. intravenous; level of hyperacetylation; duration of hyperacetylation). For example, it remains unclear whether tumor histone acetylation correlates with clinical responses, or whether pan-DACi

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which inhibit both class I and II HDACs are superior to isotype-selective HDAC's targeting class I alone. Moreover, as the functional profiles of various DACi vary substantially, there is the prospect of matching them to tumors with particular genetic profiles to improve clinical responses.

Through these affects on histones and non-histone protein targets the HDACi have a number of effects on cells. These downstream effects include cytokine signaling, cell cycle (and effects on p53), transcription factor complexes and very importantly, apoptosis. The latter can be induced by both the direct and indirect pathways with key interactions with the ubiquitin, proteasome, aggresome and NFkB systems. It is important to recognize that the anti-tumor effect involves targeting not only the tumor cell itself (including the putative cancer stem cell) but also the tumor microenvironment and patient's immune response to the tumor.

To date, most clinical studies have used single-agent DACi. Vorinostat and romidepsin have already been approved by the FDA for the treatment of relapsed and refractory cutaneous T cell lymphoma (CTCL). In this Edition the reader will discover the various other haematological malignancies where DACi have activity—Hodgkin lymphoma, peripheral T cell lymphoma (PTCL), B cell non Hodgkin lymphoma, myeloma and myeloid malignancies. Moreover, the potential synergy of DAC inhibition in combination with many chemotherapeutic and biologically active anti-cancer compounds in pre-clinical studies, suggests combination strategies should be a major focus in future studies. Diseases such as PTCL and CTCL currently have a high relapse rate after standard chemotherapy and one can envisage HDACi being incorporated in front-line studies in such diseases. Although most patients with HL are cured with up-front chemo-radiotherapy, there still is an unmet clinical need for patients who relapse following autologous stem cell transplant, and older, relapsed, patients who are not transplantation candidates. Given the CT and PET responses seen with MGCD0103 and panobinostat, it seems likely Phase II and then Phase III combination studies will follow in patients with poor prognosis disease in the up-front setting or as maintenance.

With respect to myeloid diseases, early data indicates clinical activity and whether specific molecularly-defined subgroups can predict for response or resistance needs to be a focus of future studies. Combination strategies with chemotherapy and demethylating agents are underway but only large Phase III studies will determine efficacy. Moreover, study design will need to be such that these drugs can be tested in older frailer patients to improve survival as well as examining the possibility of HDACi improving remission- and cure-rates when combined with aggressive chemotherapy in younger patients—perhaps through its potential effects on tumor stem cells. Earlier studies in myeloma highlight the potential for rationally-designed combinations such as DACi-proteasome-inhibitor combinations.

Although no major long-term toxicities have been recognized with the HDACi, one needs to recognize that there are very few patients to date who have been treated continuously for prolonged periods of time. Long-term effects will need monitoring with a focus on lymphocyte, hematopoietic, hormonal function and virus reactivation.

Finally, we need to be mindful that there is still much to be learned about the targets of these agents that lead to responses. Although biomarkers such as histone acetylation have some value in correlating dose to level and duration of hyperacetylation, it does not routinely predict for response. Indeed, it remains unclear as to whether the intensity or duration of acetylation is key to tumor response or whether off target effects such as non-histone targets are more important. Consequently, it is critical that extensive biomarker studies continue to be incorporated into all early phase clinical trials with these agents.

Responses observed to single agent HDACi's have predominantly been in advanced haematological malignancies, with few seen in solid tumors thus far. In this series of manuscripts we review the current state of understanding with an emphasis on those DACi in clinical development, and the influence of the DACi on haematological malignancies in particular.

Conflict of Interest H. Miles Prince: Medical Advisory to Novartis, Merck. Gloucester Pharmaceuticals and Celgene.

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